Feasibility of High-Gradient Magnetic Implants for Magnetic Drug Targeting

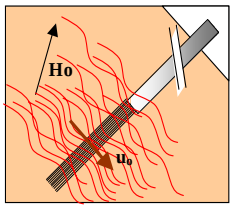
Andrea L. Stanley[1], Armin D. Ebner[1], Michael D. Kaminski[3], Axel J. Rosengart[2] and James A. Ritter[1*]

[1-3]Collaboration for Applied Nanotechnology in Medicine, [1]Department of Chemical Engineering, University of South Carolina, Columbia, SC, USA; [2]Departments of Neurology and Surgery, University of Chicago, Chicago, IL, USA; [3]Chemical Engineering Division, Argonne National Laboratory, Argonne, IL, USA; *Email: ritter@engr.sc.edu, Phone: +01-803-777-3590, Fax:+01-803-777-8265.

INTRODUCTION

- One key problem with current drug administration protocol is the difficulty associated with targeting specific areas in the body.
- Large doses of a drug are typically needed to ensure the required amount reaches the site; but such large doses inevitable cause toxic side effects at non-targeted organs.
- Hence, a very active and important area of research involves the development of drug delivery technologies that target specific sites in the body.
- One way to target a specific site is to incorporate magnetic particles into drug carriers and then to collect and retain them at the site via an externally applied magnetic field.
- However, it has been shown that an externally applied magnetic field alone may not be capable of retaining a sufficient number of drug carrier particles to justify its use.

OBJECTIVE



- This study examines the feasibility of using internally positioned (transdermally) ferromagnetic filaments, which by virtue of an external magnetic field, can significantly enhance the force on and hence retention of magnetic drug carrier particles (MDCPs) within a network of capillaries at a specific site in the body above that which would occur without the filament present[1].
- The principle being exploited is the same as that used in high gradient magnetic separation (HGMS) processes for the removal of small and weakly magnetic particles.
- The variables investigated include the blood velocity (u_o = 0.05 - 0.5 cm/s), the size (R_w = 25 - 100 μm radius) and separation of the filaments (409 SS, $M_{w,s}$ = 1357 kA m^{-1}), the size (R_p = 0.2 - 2.0 μm radius) and content of magnetite ($M_{fm,p}$ = 455 kA m^{-1}) in the MDCPs ($x_{fm,p}$ = 5 - 40 wt%), and the magnetic field strength ($\mu_o H_o$ = 0.0 - 2.0 T).

SCHEMATIC

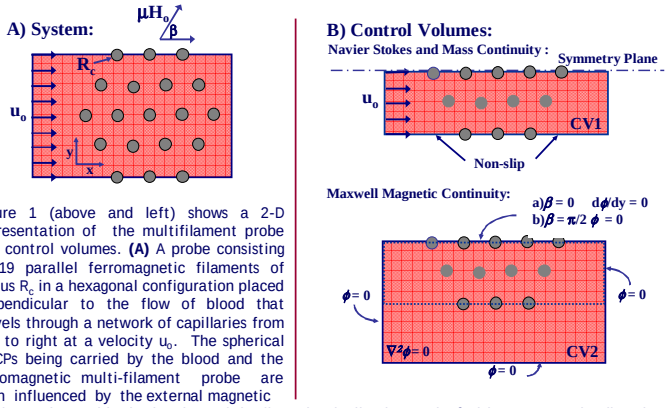


Figure 1 (above and left) shows a 2-D representation of the multifilament probe and control volumes. **(A)** A probe consisting of 19 parallel ferromagnetic filaments of radius R_c in a hexagonal configuration placed perpendicular to the flow of blood that travels through a network of capillaries from left to right at a velocity u_o. The spherical MDCPs being carried by the blood and the ferromagnetic multi-filament probe are both influenced by the external magnetic field $\mu_o H_o$ that resides in the plane of the figure but inclined at angle β with respect to the direction of the blood flow. **(B)** Two different control volumes (CV) are used for determining the capture of the MDCPs by the ferromagnetic filaments. CV1 is used to determine the x-y components of the blood velocity by solving the Navier-Stokes and mass continuity equations. CV2 is used to solve Maxwell's continuity equation for the magnetic flux **B**. To reduce computational costs, only the bottom half of the system depicted in (A) is evaluated in both CVs.

DESCRIPTION/ASSUMPTIONS

CV1:

- A plane of symmetry is applied as a boundary condition, where the system is divided into two equal sections.
- The flow of the blood through the capillary network behaves like a simple viscous fluid.
- Non-slip boundary conditions are assumed at the surface of every filament.
- Non-slip boundary conditions are assumed at the bottom border to ensure the blood flows through the spaces between the filaments.
- Blood uniformly enters CV1 at a velocity u_o that is parallel to the x direction.

CV2:

- The magnetic flux **B** is represented in terms of the gradient of a scalar magnetic potential ϕ, which is defined differently in the regions corresponding to the filaments and the fluid.
- Except for the upper boundary, the other three borders are placed far enough from the filaments to set $\phi = 0$ as a boundary condition.
- At the upper border the boundary condition for ϕ depends on the angle β of the magnetic field. Due to pure symmetrical reasons, for the orientation defined by $\beta = 0$ and $\pi/2$, the boundary conditions at this upper border are $d\phi/dy = 0$ and $\phi = 0$, respectively

PARTICLE TRAJECTORY EQUATIONS

The trajectory lines (or streamlines) of the MDCPs, defined by their velocity components, $v_{p,x}$ and $v_{p,y}$, are determined by the dynamic equilibrium between two main forces, i.e., the drag and magnetic forces. Both the gravitational and inertial forces (i.e., those involving particle acceleration) are neglected, as they are relatively small compared to the other two forces in an aqueous system at the length scales investigated here. The magnetic-drag force balance leads to the following expressions for the two components of the MDCP velocity[1]:

$$v_{p,x} = v_x + \frac{V_{m,p}}{u_o M_w H}\left[\left(\frac{1}{R_w}\frac{\partial\phi}{\partial\xi_x} - H_o\cos\beta\right)\frac{1}{R_w}\frac{\partial^2\phi}{\partial\xi_x^2} + \left(\frac{1}{R_w}\frac{\partial\phi}{\partial\xi_y} - H_o\sin\beta\right)\frac{1}{R_w}\frac{\partial^2\phi}{\partial\xi_x\partial\xi_y}\right]$$

$$v_{p,y} = v_y + \frac{V_{m,p}}{u_o M_w H}\left[\left(\frac{1}{R_w}\frac{\partial\phi}{\partial\xi_x} - H_o\cos\beta\right)\frac{1}{R_w}\frac{\partial^2\phi}{\partial\xi_x\partial\xi_y} + \left(\frac{1}{R_w}\frac{\partial\phi}{\partial\xi_y} - H_o\sin\beta\right)\frac{1}{R_w}\frac{\partial^2\phi}{\partial\xi_y^2}\right]$$

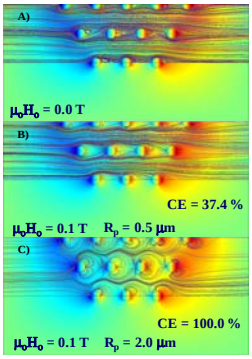
$$V_{m,p} = \frac{2}{9}R_p^2\omega_{fm,p}\frac{\mu_o}{R_w\eta_B}M_w M_{fm,p} \qquad M_w = 2\alpha_w H_o \qquad M_{fm,p} = 3\alpha_{fm,p}H$$

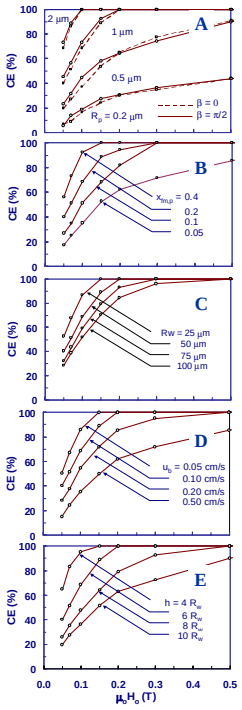
$$H = |\mathbf{H}_o - \nabla\phi| \qquad \alpha_w = \min\left(1, \frac{M_{w,s}}{2H_o}\right) \qquad \alpha_{fm,p} = \min\left(1, \frac{M_{fm,p,s}}{3H}\right)$$

The components of the blood velocity, v_x and v_y, were obtained previously by solving the Navier Stokes and Continuity equations in CV1. The scalar magnetic potential ϕ was obtained by solving Maxwell's equation $\nabla^2\phi = 0$ in CV2.

TYPICAL SIMULATION RESULTS

Figure 2 (right) shows dynamic simulations (obtained using the FEMLAB platform) of the MDCPs flowing through the multifilament probe in a fluid that represents blood in a capillary system. Although this overly simplified depiction of blood flow in a capillary system is not very realistic, it is considered to be a very conservative representation, since better results are expected in a system where the blood flow is restricted by the complex capillary network. Figure A shows the streamlines of the blood flowing at u_o = 0.1 cm s^{-1} with the external magnetic field $\mu_o H_o$ off, (i.e., $\mu_o H_o$ = 0.0 T) and for filaments with R_w = 50 μm, MDCPS with $x_{fm,p}$ = 0.2, and an inter-filament spacing R_{w-w} = 6R_w mm. In this case, the MDCPs simply follow the streamline patterns defined by the moving fluid. Figures B and C show the MDCP streamlines obtained with $\mu_o H_o$ = 0.1 T for two different MDCP radii (R_p). The fraction of the streamlines captured by the probe represents its collection efficiency (CE), with CEs of 0, 37.4, and 100% in cases A, B, and C, respectively.





COLLECTION EFFICIENCY RESULTS

Figure 3 (left) provides the results from a parametric study on the CE of the multi-filament ferromagnetic probe. The CE is plotted as a function of the magnetic field strength $\mu_o H_o$ and for different A) MDCP radii R_p, B) magnetite contents $x_{fm,p}$, C) individual filament radii R_c, D) blood velocities u_o, and E) inter-filament spacings R_{c-c}. Unless specified in the graph, the other conditions are: R_w = 50 μm, R_{c-c} = 8R_c, R_p = 1.0 μm, $x_{fm,p}$= 0.2 and u_o = 0.1 cm/s. The results show very convincingly that large CEs are easily attainable over a wide range of entirely feasible conditions. The main reason for these surprisingly good results is the slow velocity used in the simulations, which is typical of blood flow in capillaries (i.e., 0.1 cm s^{-1}). However, excellent results are realized even for blood velocities of 0.5 cm/s. It is noteworthy that these very promising results (some showing 100% CEs) are being obtained with MDCPs that have a relatively low content of magnetite and at magnetic field strengths that are considered to be low (< 0.5 T). These results also indicate that it may be entirely possible to attach tiny magnets to the tip of the probe that are only slightly larger than the filaments themselves for the magnetic filed source in this MDT approach.

CONCLUSIONS

- This exploratory study showed very convincingly that the proposed MDT system, utilizing the ferromagnetic multi-filament probe concept to increase the magnetic force on the magnetic drug carrier particle, has considerable promise as an effective drug-targeting tool.
- Although the technique is mildly invasive, since it requires the insertion of a needle or syringe, it may offer significant advantages over the traditional non-invasive methods for collecting MDCPs at a site, such as the application of an external magnet alone.
- The magnetic field source and the ferromagnetic multi-filament probe may be combined for ease of implementation.

AKNOWLEDGEMENTS

- The partial research support provided by the following institutions and agencies was greatly appreciated: the Brain Research Foundation, Biological Science Division, The University of Chicago and Pritzker School of Medicine, the Cancer Research Foundation, Chicago, IL, the National Science Foundation under grant No. CTS-0314157, the Defense Advanced Research Projects Agency's BioMagnetICs program under contract 8c85000107, and The USC NanoCenter.

REFERENCE

[1]J.A. Ritter, A.D. Ebner, K.D. Daniel, and K.L. Stewart, "Application of High Gradient Magnetic Separation Principles to Magnetic Drug Targeting," *J. Mag. Mag. Mat.*, in press on-line (2004).

COLLABORATIVE INVESTIGATORS FOR APPLIED NANOTECHNOLOGY IN MEDICINE